



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

PATENTEE: Phillips, J.) ATTORNEY DOCKET: 05112945
PATENT.: 6,699,885)
CONTROL NO.: 90/007,686) GROUP ART UNIT: 3991
TITLE: Substituted Benzimidazole Dosage Forms And Methods Of Using Same
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Sir:

AMENDMENT AND RESPONSE TO OFFICE ACTION DATED MARCH 24, 2006

This communication is responsive to the Office Action dated March 24, 2006. Further examination of the application is respectfully requested after entry of the amendments proposed herein. This response is made within two months of the mailing date of the present Office Action; accordingly, no fee is believed payable in respect of this communication. If any fee is deemed payable, please charge such a fee to Deposit Account No. 13-0019. Patentee respectfully requests amendment of the patent and reconsideration and allowance of the amended and newly pending claims.

Docket No. 05112945

Amendments to the Claims are reflected in the listing of claims, which begin on page 3.

Remarks/Arguments begin on page 5.

Conclusion is on page 22.

IN THE CLAIMS

Please enter the following claim amendments.

1. (Amended) A method of treating a gastric acid related disorder in a subject in need thereof, comprising:

providing a solid pharmaceutical composition for oral administration to the subject, the composition consisting essentially of: (a) a therapeutically effective amount of at least one acid labile, substituted benzimidazole H⁺, K⁺-ATPase proton pump inhibitor; (b) at least one buffering agent in an amount of about 0.1 mEq to about 2.5 mEq per mg of proton pump inhibitor; and (c) one or more optional pharmaceutically acceptable excipients, wherein at least some of the proton pump inhibitor is not enteric coated and the solid pharmaceutical composition has a total buffering agent to total proton pump inhibitor weight ratio of greater than 20:1; and

orally administering the pharmaceutical composition to the subject,

wherein upon oral administration of the pharmaceutical composition to the subject, an initial serum concentration of the proton pump inhibitor greater than about 0.1 µg/ml is obtained at any time within about 30 minutes after administration of the composition.

26. (Amended) A method of treating a gastric acid related disorder in a subject in need thereof, comprising:

providing a pharmaceutical composition consisting essentially of [orally administering to the subject a single dose of a solution or suspension of a pharmaceutical composition, the composition consisting essentially of:] (a) a therapeutically effective amount of at least one acid labile, substituted benzimidazole H⁺, K⁺-ATPase proton pump inhibitor in powder form; (b) at least one buffering agent in powder form and in an amount of about 0.1 mEq to about 2.5 mEq per mg of proton pump inhibitor; and (c) one or more optional pharmaceutically acceptable excipients, wherein at least some of the proton pump inhibitor is not enteric coated and the solid pharmaceutical composition has a total buffering agent to total proton pump inhibitor weight ratio of greater than 20:1;

mixing the pharmaceutical composition with a liquid to form a solution or suspension;

and

orally administering a single dose of the solution or suspension to the subject, wherein an initial serum concentration of the proton pump inhibitor greater than about 0.1 µg/ml is obtained

at any time within about 30 minutes after administration of the solution or suspension [composition,] and wherein the administration step does not require further administration of the buffering agent(s) beyond that administered in the single dose.

52. (New) The method of claim 1 wherein the proton pump inhibitor is selected from omeprazole, lansoprazole, rabeprazole, esomeprazole, pantoprazole or an enantiomer, isomer, free-base or salt thereof.

53. (New) The method of claim 26 wherein the proton pump inhibitor is selected from omeprazole, lansoprazole, rabeprazole, esomeprazole, pantoprazole or an enantiomer, isomer, free-base or salt thereof.

REMARKS/ARGUMENTS

Claims 1 - 51 are patented and claims 52 and 53 are pending. By the present amendment, two claims of U.S. Patent No. 6,699,885 (the " '885 Patent") are amended. Support for amended claim 1 can be found at least at Col 8, ll. 56-60 of the '885 Patent. Support for amended claim 26 can be found at least at Col 8, ll. 56-60, Col. 19, ll. 59 – 64, and Col. 21, ll. 29 - 40 of the '885 Patent. Also by the present amendment, Claims 52 and 53 are added. Support for new Claims 52 and 53 can be found at least at Col. 9, ll. 57-65, Col. 11, ll. 32-61, Col. 16, ll. 62-65, and Col. 61, l. 67 to Col. 62, l. 7. None of the amendments proposed herein enlarge the scope of the claims of the patent or introduce new matter.

Fees for two (2) dependent claims are deemed payable. Accordingly, a check in the amount of \$50 is enclosed pursuant to 37 C.F.R. 1.20(c)(4).

As detailed below, Patentee submits that no *prima facie* case of anticipation or obviousness has been established.

A. NO PRIMA FACIE CASE ESTABLISHED UNDER 35 U.S.C. §§ 102 OR 103

The claimed invention has distinct advantages over the Depui, Horowitz, Carroll, Nomura and other references cited by the Examiner. Patentee and its exclusive licensee, Santarus, Inc., have generated data – and real-world clinical proof – demonstrating the advantages of the claimed invention over those in the references cited by the Examiner. The claimed invention has been approved by the FDA and is currently marketed in the United States by Santarus as Zegerid® Capsules and Powder for Oral Suspension. Referring to the Zegerid® Package Insert (attached as Exh. 1), the claimed invention not only provides 24 hour control of gastric acid, it also provides immediate release of omeprazole and maximal blood levels within 30 minutes as compared to Prilosec®'s delayed-release mechanism (Exh. 2).

Moreover, as detailed below, none of the references cited by the Examiner, either alone or in combination, anticipate or render obvious Patentee's claimed invention. For example, with respect to one or more pending claims:

- The references relied on by the Examiner do not teach or suggest a pharmaceutical composition in either a powder form or a solid dosage form comprising a proton pump inhibitor ("PPI") and buffering agent as claimed by Patentee

- The references relied on by the Examiner do not teach or suggest the pharmacokinetic properties of the PPI and buffer compositions claimed by Patentee
- The Examiner's reliance on Horowitz to illustrate the blood level of Depui's enteric coated formulations, Carroll's crushed enteric granules, and Nomura's compositions is misplaced
- The references relied on by the Examiner teach away from compositions with a total buffering agent to total PPI weight ratio of greater than 20:1 as claimed by Patentee
- The references relied on by the Examiner teach away from employing non-enteric coated PPI plus buffer to treat gastric acid related disorders
- There was no reasonable expectation at the time of the invention that the combination of references relied on by the Examiner would successfully result in the invention claimed by Patentee
- The references relied on by the Examiner fail to teach the motivation, desirability or interchangeability of their teachings
- The Examiner's suggestion that without any specific guidance the skilled person could pick and choose from an almost infinite number of formulation possibilities presented in the references relied on by the Examiner to arrive at Patentee's claimed invention is random, speculative and based on the use of impermissible hindsight
- Even if combined, the references relied on by the Examiner, alone or in combination with one another, fail to teach or suggest each element of the claimed invention
- "Secondary considerations" confirm the non-obviousness of the claimed invention, e.g., proceeding contrary to accepted wisdom and license showing industry respect for the invention claimed.

I. Rejection Of Claims 1-11, 14 And 19-25 Under 35 U.S.C. § 102(b) As Allegedly Anticipated By Depui, As Evidenced By Horowitz

Claims 1-11, 14, and 19-25 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by WO 97/25066 (hereinafter "Depui") as evidenced by Horowitz. Patentee respectfully traverses this rejection.¹

MPEP § 2131 provides that "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described in a single prior art

¹ Patentee points out the Depui reference citation is missing a numeral in the Office Action (*See, e.g.*, Office Action at p. 6) and it is not listed on the Form 892 Notice of References Cited. Patentee presumes that the Examiner is referring to WO 97/25066 and has proceeded based on this assumption. However, clarification of the record on this point is respectfully requested.

reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Furthermore, "[t]he identical invention must be shown in as complete detail as contained in the...claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236-9 USPQ2d 1913, 1920 (Fed. Cir. 1989). Lastly, "the elements must be arranged as required by the claim...." *In re Bond*, 910 F.2d 831, 15 USPQ2d 1566 (Fed. Cir. 1990).

First, Depui states that its enteric coated formulations do not disintegrate in the stomach. Therefore, one would not expect that Depui's formulations would meet the pharmacokinetic ("PK") limitations of Patentee's claims. For example, Depui specifically states that its enteric coating makes "the pellets of the dosage form *insoluble in acidic media*, but disintegrating/dissolving in near neutral to alkaline media such as, for instance the liquids present in the proximal part of the small intestine, where dissolution of the proton pump inhibitor is desired" (emphasis added). Depui at p. 20, ll. 25-28. Additionally, Depui teaches that the "enteric coating layer(s) covering the individual units of the acid susceptible proton pump inhibitor has properties such that the compression of the units into a tablet does not significantly affect the acid resistance of the individually enteric coating layered units." *Id.* at p. 5, ll. 19-22. Moreover, Depui states:

If the enteric coating layer does not withstand the compression of the pellets into a tablet the susceptible active substance will be destroyed upon administration by penetrating acidic gastric juice, i.e., the acid resistance of the enteric coating layer of the pellets will not be sufficient in the tablet after compression.

Id. at p. 4, ll. 8-11. Based on these admonitions, the skilled person at the time of the invention would not have expected absorption of the PPI from Depui's enteric coated compositions to occur within 30 minutes as claimed. As such, Depui fails to teach all the limitations of claims 1-25, expressly or inherently and, therefore, does not anticipate these claims.

Second, Patentee has amended claim 1 to include the limitation that "at least some of the proton pump inhibitor is not enteric coated," which is also not taught by Depui. In fact, Depui specifically teaches away from compositions comprising proton pump inhibitor that is not enteric coated:

Some gastric acid suppressing agents, such as proton pump inhibitors, are susceptible to degradation/transformation in acid reacting and neutral media. In respect of the stability properties, *it is obvious* that one of the active substances being a proton pump

inhibitor *must* be protected from contact with acid gastric juice by an enteric coating layer.

Depui at p. 3, ll. 25-28 (emphasis added).

Third, Depui does not disclose a composition having “a total buffering agent to total proton pump inhibitor weight ratio of greater than 20:1” as required by the amended claims. In fact, the only disclosure of the amount of buffer useful in Depui’s compositions arises from the examples which only disclose total buffering agent to total PPI weight ratios of up to 2:1. *See, e.g.,* Example 1 which has a total buffering agent to total PPI weight ratio of about 0.04:1; Example 2 which has a total buffering agent to total PPI weight ratio of about 0.025:1; and Example 3 which has a total buffering agent to total PPI weight ratio of about 2:1. This is not surprising considering Depui was not using the buffering agent to protect the PPI from degradation in gastrointestinal fluid. Rather, Depui discloses the use of these smaller amounts of buffer to “provide immediate symptom relief” to the patient while waiting for the enteric coated proton pump inhibitor to pass through the stomach. Depui, at p. 3, ll. 11-14.

Fourth, the Examiner’s reliance on Horowitz as allegedly illustrating Patentee’s claimed blood level limitation not mentioned in Depui, *i.e.* an “initial serum concentration of the proton pump inhibitor greater than 0.1 µg/ml . . . within about 30 minutes after administration,” is misplaced for at least the following reasons.

As set forth in § 2131.01 III of the MPEP, in order to make a showing of inherency, the *evidence* must make clear that the missing descriptive matter is *necessarily present* in the thing described in the reference, and that it would be so recognized by persons of ordinary skill” (emphasis added). Horowitz is directed to *liquid, non-enteric coated* compositions. Depui, on the other hand, is directed to *solid, enteric coated* compositions. As described above, Depui’s dosage forms are enteric coated with a material that makes the PPI “insoluble in acidic media, but disintegrating/dissolving in near neutral to alkaline media such as, for instance the liquids present in the proximal part of the small intestine, where dissolution of the proton pump inhibitor is desired.” Depui at p. 20, ll. 25-28. As such, the enteric coated PPI would not be available for absorption until after the enteric coated PPI passes through the stomach and enters the small intestine. Consequently, it is speculative at best to compare Depui’s solid forms to Horowitz’s liquid dosage forms.

Moreover, Horowitz employs about 3,700 mg of sodium bicarbonate per 90 mg of omeprazole—an amount of buffer that could not practically be used in a solid dosage form. Depui, on the other hand only discloses a total buffering agent to total PPI weight ratio of up to about 2:1 (or 180 mg buffer per 90 mg omeprazole). To assume that 180 mg of sodium bicarbonate would provide the same protection of a PPI in gastric acid as 3,700 mg is speculative. Therefore, Horowitz cannot be used to demonstrate the pharmacokinetic characteristics of Depui's enteric coated compositions.

Further, it is well known that a given drug substance will have different absorption rates and times of onset depending on the dosage form and excipients, and that these differences are a function of both the formulation and the route of administration. *See e.g.* Ansel et al., Pharmaceutical Dosage Forms and Drug Delivery Systems, Williams & Wilkins, 1995, pp. 77 (attached as Exh. 3). ("An individual drug substance may be formulated into multiple dosage forms which result in different drug absorption rates and times of onset, peak, and duration of action."). This is because, for example, a solid dosage form must first disintegrate and then dissolve before the PPI is released, and only after this occurs can the PPI be absorbed (assuming that it has not been degraded by stomach acid). Thus, Horowitz's liquid disclosure provides no meaningful evidence relevant to the PK performance of Depui's solid dosage form, and the Examiner's anticipation rejection should be withdrawn.

Indeed, Depui and Horowitz not only fail to anticipate, but actually teach away from the claimed invention: Depui informs one to enteric coat, and Horowitz discloses that for clinical use the omeprazole would be formulated in enteric coated granules and not administered with bicarbonate. *See* Horowitz at p. 793. Thus, when the teachings of Depui and Horowitz are taken as a whole, as is required when examining potential prior art references, each of them teach away from the use of a solid dosage form comprising non-enteric coated PPI and buffer as claimed by Patentee.

For the foregoing reasons, Patentee submits that no *prima facie* case of anticipation has been established and respectfully requests withdrawal of this rejection.

II. Rejection Of Claims 26-35, 37-42 And 47-51 Under 35 U.S.C. § 102(b) As Allegedly Anticipated By Carroll As Evidenced By Horowitz And Dhanoa

Claims 26-35, 37-42, and 47-51 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Carroll as evidenced by Horowitz and Dhanoa². Since each limitation of Claim 26 is not expressly or inherently described in Carroll, the Examiner's burden of establishing a *prima facie* case of anticipation has not been met. Thus, Patentee respectfully requests withdrawal of this rejection.

Claims 26-51 require the step of providing a pharmaceutical composition "in powder form" which consists essentially of "at least one acid labile, substituted benzimidazole H+, K+-ATPase proton pump inhibitor" and "at least one buffering agent." In contrast, Carroll discloses the addition of crushed enteric coated pellets to *pre-made* sodium bicarbonate *solution*. Thus, Carroll does not disclose a pharmaceutical composition in powder form that has in it both proton pump inhibitor and buffering agent. For at least this reason, each and every element of Patentee's claimed invention is not present in Carroll, and no *prima facie* case of anticipation is established.

Moreover, Carroll teaches the delivery of an omeprazole suspension via a nasogastric tube and provides the following description for making the composition administered: (1) open the Prilosec® capsules containing enteric coated pellets, (2) crush the pellets, and (3) mix the *crushed pellets* with 25 cc of sodium bicarbonate solution (1 mEq per ml). Therefore, not only does Carroll fail to teach a powder containing both PPI and buffering agent, there is no evidence that Carroll's non-uniform slurry would naturally result in an "initial serum concentration of the proton pump inhibitor greater than 0.1 µg/ml . . . within about 30 minutes after administration" as claimed by Patentee. For example, if the composition was not sufficiently crushed, the enteric coating would still be intact and would likely prevent absorption of the PPI in the stomach thereby delaying the absorption of the PPI until sometime after 30 minutes. In fact, Carroll itself suggests this by stating that the "crushed pellets" are administered, indicating that enteric coating may still be intact on the PPI. Moreover, even if the enteric pellets were crushed, they would still need to be stirred in the bicarbonate solution for a sufficient period of time so as to allow the

² Dhanoa is not material to Patentee's claims because it is directed to unrelated cyclic renin inhibitors and their use in treating renin-associated hypertension.

enteric coating to dissolve in order for the omeprazole to be available for absorption in the stomach. Carroll is silent as to any stirring step.

Additionally, as described in inventor Dr. Jeffery O. Phillips' Declaration (attached as Exh. 4), employing the Carroll method results in an undefined, non-homogeneous slurry rather than a uniform solution or suspension. Likewise, using crushed pellets similar to the above does not appear to work:

In one case, the omeprazole enteric-coated pellets had not completely broken down before the administration of the first two doses, which produced an erratic effect on gastric pH. The gastric pH increased to >5 as soon as the patient was given a dose of simplified omeprazole suspension (in which the enteric-coated pellets of omeprazole had been allowed to completely break down).

Phillips *et al.*, "A Prospective Study of Simplified Omeprazole Suspension for the Prophylaxis of Stress-Related Mucosal Damage," Crit. Care Med. Vol. 24(ii): 1793-1800, 1795 (1996) (attached as Exh. 5).

Thus, Carroll's procedure prevents a finding of inherency because practicing this disclosure would not naturally result in an "initial serum concentration of the proton pump inhibitor greater than 0.1 µg/ml . . . within about 30 minutes after administration." See *Geneva Pharmaceuticals, Inc. v. GlaxoSmithKline PLC*, 189 F.Supp. 2d 377 (Fed. Cir. 2002) ("A reference includes an inherent characteristic if that characteristic is the 'natural result' flowing from the reference's explicitly explicated limitations").

Horowitz and Dhanoa fail to cure the deficiencies of Carroll. Neither of Horowitz or Dhanoa teaches a method that includes a step of providing a pharmaceutical composition consisting essentially of (a) a therapeutically effective amount of at least one acid labile, substituted benzimidazole H⁺, K⁺-ATPase proton pump inhibitor in powder form and (b) at least one buffering agent in powder form. Moreover, unlike Carroll, where crushed enteric coated omeprazole granules were combined with a single dose of 25 mEq of sodium bicarbonate solution, Horowitz discloses the administration of 300 ml of a 160 mmol/l of sodium bicarbonate solution (about 48 mEq of sodium bicarbonate) in divided doses, before, together with and for 30 minutes after administration of uncoated omeprazole. There is simply no evidence in Horowitz suggesting that the claimed PK profile would naturally result if one used a single dose of 25 mEq of sodium bicarbonate as used in Carroll's slurry.

On the contrary, the marked differences between the Carroll and Horowitz disclosures demonstrate that the skilled artisan lacked the essential information necessary to take the Examiner's theory out of the realm of hindsight speculation to one where the claimed PK limitation was necessarily present. The Horowitz study was not undertaken to produce an effective non-enteric coated PPI formulation, but rather was a study to determine the effect of larger doses of omeprazole on gastric emptying times. *See* Horowitz at abstract. For purposes of this study, Horowitz administered 90 mg of uncoated omeprazole with multiple doses of sodium bicarbonate solution. However, for clinical use, Horowitz disclosed that omeprazole would be formulated in enteric coated granules and not administered with sodium bicarbonate. Carroll, on the other hand, was simply trying to administer crushed enteric coated granules down a nasogastric (NG) tube. Both references have technical shortcomings, namely Carroll's non-uniform slurry was likely prone to clog NG tubes and Horowitz's method involved large and potentially dangerous amounts of sodium bicarbonate, which is likely why the clinical formulation would be enteric coated and administered without sodium bicarbonate.

For the foregoing reasons, Patentee submits that no *prima facie* case of anticipation has been established and respectfully requests withdrawal of this rejection.

III. Rejection Of Claims 36-37 And 43-46 Under 35 U.S.C. § 103(a) As Allegedly Unpatentable Over Carroll (As Evidenced By Horowitz And Dhanoa) And Further In View Of Nomura

Claims 36-37 and 43-46 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Carroll as evidenced by Horowitz and Dhanoa (as applied to claims 26-35, 37-42 and 47-51) and further in view of Nomura. Patentee traverses this rejection.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings. Second, there must be a reasonable expectation of success. That is, the hypothetical person of ordinary skill in the art, at the time the invention was made, must have had a reasonable expectation that the proposed modification or combination would work to produce beneficial results. Finally, the references when combined must teach or suggest all the claim limitations. *See* MPEP § 2143. The burden of establishing a *prima facie* case of obviousness lies with the Examiner, and both the suggestion and the expectation of success must be found in the prior art, not the Patentee's disclosure." *In re Dow Chemical*, 5 USPQ 2d 1531

(Fed. Cir. 1988). Since there would have been no motivation to combine Carroll with Nomura in such a manner as to arrive at the claimed invention, withdrawal of this rejection is respectfully requested.

The infirmities of Carroll, Horowitz and Dhanoa have been discussed above. Patentee respectfully submits that the combination of Carroll with Nomura is improper at least because Nomura teaches away from the combination of these two references. MPEP § 2146 clearly states that “[i]t is improper to combine references where the references teach away from their combination.” *See In re Grasselli*, 713 F.2d 731 (Fed. Cir. 1983). Nomura teaches that the total basic material to anti-ulcer compound weight ratio must be less than 20:1, preferably between about 1.1:1 and 10:1, even more preferably between about 2.1:1 and 5:1. Nomura at p. 6, ll. 17-21. Specifically, “if the amount of basic material is too large, the administration of the composition is disturbed.” *Id.* at p.6, ll. 20-21. Both Carroll and Horowitz, on the other hand, only disclose total buffering agent to total PPI weight ratios of greater than 20:1. As such, Nomura teaches away from any combination with Carroll or Horowitz and Dhanoa, and no *prima facie* case of obviousness exists.

Furthermore, it is well settled that where a proposed combination would render one or more references inoperable for its intended purpose, the references are considered to teach away from their proposed combination and no motivation to combine exists. See MPEP §2143.01 V., and *In re Gordon*, 733 F.2d 900 (Fed. Cir. 1984). In this case, Carroll discloses the nasogastric administration of liquid compositions containing crushed enteric coated omeprazole granules which have been mixed with sodium bicarbonate solution. The purpose of the experiments described by Carroll was to overcome “difficulties with nasogastric tube delivery of omeprazole.” However, Nomura is directed to compositions that are to be administered orally (not through a nasogastric tube; p. 6, ll. 28). The dosage forms disclosed by Nomura (tablets, pellets, capsules, powder, granules, syrup and paste) are not suitable for administration via a nasogastric tube because they would be too large and inflexible to fit down the lumen of a nasogastric tube or would plug the exit hole of the nasogastric tube, or in the case of a syrup would be so viscous as to clog the tube. *See, e.g.*, “Guidelines for the Management of Enteral Tube Feeding in Adults,” (attached as Exh. 6) (published by the Clinical Resource Efficiency Support Team, April 2004), particularly page 51 indicating that viscous fluids such as syrups cause difficulties when administered down nasogastric tubes.

Therefore, the proposed combination of Carroll with Nomura would destroy the intended function of Carroll's composition—namely, nasogastric tube administration. As such, these references teach away from their combination and no *prima facie* case of obviousness exists.

It is also settled law that where a proposed combination would change the principles under which a reference was designed to operate, the teachings of the references are not sufficient to render the claims *prima facie* obvious. See, e.g., MPEP §2143.01 VI.; *In re Ratti*, 7270 F.2d 810 (CCPA 1959). Because Nomura's compositions are stated to operate via oral delivery (see Nomura at p. 6, l. 28: “[t]he anti-ulcer composition according to the present invention is administered *orally* to human beings” (emphasis added)), and Carroll's method operates via nasogastric delivery, the combination of these references would impermissibly change the principle of operation of one or both references.

Moreover, the skilled person would not have had a reasonable expectation of success at the time of Patentee's invention. Patentee submits that the teachings in Nomura – *i.e.*, that administration of the drug is disturbed when the weight ratio of total basic material to total active agent is greater than 20:1 — would have prevented one of skill in the art at the time of Patentee's invention from having any reasonable expectation that the claimed invention, which requires a total buffering agent to total PPI weight ratio of greater than 20:1, would work. Thus, Patentee respectfully requests withdrawal of this rejection.

Although Patentee believes that the combination of Nomura and Carroll is improper for the reasons set forth above, even if combined, these references fail to teach or suggest all the claimed limitations and, therefore, cannot establish a *prima facie* case of obviousness. Again, Carroll does not teach or suggest a composition which provides an “initial serum concentration of the proton pump inhibitor of greater than 0.1 µg/ml . . . within about 30 minutes after administration” as required by Patentee's claims because (1) the evidence offered by the Examiner, *i.e.*, Horowitz, fails to demonstrate that the missing PK limitation is necessarily present in Carroll, and (2) the PK limitation in the claims is not a property that is “necessarily present” upon administration of Carroll's crushed enteric coated compositions as is required for a finding of inherency. Moreover, neither Carroll nor Horowitz teach or suggest a method comprising a step of providing a pharmaceutical composition “in powder form” which consists essentially of “at least one acid labile, substituted benzimidazole H⁺, K⁺-ATPase proton pump inhibitor” and “at least one buffering agent.”

For the foregoing reasons, Patentee submits that no *prima facie* case of obviousness has been established and respectfully requests withdrawal of this rejection.

IV. Rejection Of Claims 12-13 And 15-18 Under 35 U.S.C. 103(a) As Allegedly Unpatentable Over Depui, As Evidenced By Horowitz As Applied To Claims 1-11, 14, 19-25, And Further In View Of Martindale.

Claims 12-13 and 15-18 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Depui, as evidenced by Horowitz as applied to claims 1-11, 14, 19-25, and further in view of Martindale. Patentee traverses this rejection.

Although Patentee believes that the combination of Depui and Martindale is improper, even if combined, these references fail to teach or suggest all the claimed invention as a whole and, therefore, cannot establish a *prima facie* case of obviousness.

Claims 12-13 and 15-18 are dependent on claim 1 and thus necessarily include all the limitations of that claim. Thus, as discussed in § I. *supra*, each and every element of claims 12-13 and 15-18 are not set forth in Depui and Martindale. For example, claims 12-13 and 15-18 require that “at least some of the proton pump inhibitor is not enteric coated.” However, neither Depui nor Martindale disclose a composition having any amount of proton pump inhibitor that is not enteric coated. Depui is directed exclusively to enteric coated compositions while Martindale is directed only to sodium bicarbonate with no mention of proton pump inhibitors whatsoever. Additionally, claims 12-13 and 15-18 require that upon administration, the composition have an “initial serum concentration of the proton pump inhibitor of greater than 0.1 µg/ml . . . within about 30 minutes.” Yet, neither Depui nor Martindale expressly or inherently disclose this limitation.

For the foregoing reasons, Patentee submits that no *prima facie* case of obviousness has been established and respectfully requests withdrawal of this rejection.

V. Rejection Of Claims 1-25 Under 35 U.S.C. 103(a) As Allegedly Unpatentable Over Nomura In View Of Horowitz

Claims 1-25 stand rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Nomura in view of Horowitz. This rejection is respectfully traversed.

It is well settled in the law that teaching away of prior art is a strong indication of nonobviousness. *See, e.g., In re Soni*, 54 F.3d 746 (Fed. Cir. 1995). A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged

from following the path set out in the reference or would be led in a direction divergent from that which Patentee took. *See In re Gurley*, 27 F.3d 551 (Fed. Cir. 1994).

Nomura discloses compositions comprising a weight ratio of its basic material to anti-ulcer compound of *not more than* 20:1 (2000 weight parts of basic material per 100 weight parts of imidazole derivative). *See, e.g.*, Nomura at p. 5, ll. 17-21. In preferred embodiments, Nomura desires even less basic agent, for example 10:1 and more preferably 2.2:1. *Id.* Moreover, all of Nomura's examples have weight ratios of total basic material to total active agent of 5:1 or less. Thus, if motivated at all from Nomura's disclosure, the skilled artisan at the time of the invention would only have been motivated to make a composition with a total buffering agent to total active agent weight ratio of less than 20:1, not greater than 20:1 as claimed by Patentee. Nomura also teaches away from the claimed invention, which requires a weight ratio of total buffering agent to total proton pump inhibitor of greater than 20:1 *and* rapid delivery of the PPI, because Nomura teaches that "if the amount of basic material is too large, the administration of the composition is disturbed." Nomura at p. 6, ll. 20-21

The Examiner states that the claim limitation requiring that the "initial serum concentration of PPI obtained at any time within about 30 minutes after administration is greater than about 0.1 mg/ml," although not disclosed in Nomura, is an intrinsic property in view of Horowitz. Again, however, Horowitz, which is directed only to an omeprazole suspension, provides no indication or suggestion of the PK performance of Nomura's compositions. As discussed above, the pharmacokinetic profile of a liquid dosage form of a compound does not demonstrate an inherent pharmacokinetic property of other dosage forms, including solid dosage forms. Moreover, the variability in the amount of buffer disclosed in Horowitz vs. Nomura makes it speculative, at best, as to what PK profiles result from Nomura's compositions. As such, the PK performance of a solid pharmaceutical composition as presently claimed was heretofore *unknown* and unpredictable prior to Patentee's invention.

Here, based on Nomura's cautionary instruction, the skilled person would not have practiced a composition having a total buffering agent to total PPI weight ratio of greater than 20:1, especially when trying to achieve rapid uptake of the proton pump inhibitor as required by Patentee's claims. Thus, Nomura teaches away from Patentee's claimed invention.

Moreover, it is well settled in the law that inherency and obviousness are distinct concepts, and that obviousness cannot be predicated on what is *unknown*. *In re Spormann* 363

F.2d 444 (CCPA 1966) and *In re Dillon*, 919 F.2d 688 (Fed. Cir. 1990) (en banc). Thus, the Examiner's reliance on inherency in formulating an obviousness rejection is improper.

Finally, even if combined, Nomura and Horowitz, alone or in combination, do not teach or suggest each element of the claimed invention. As discussed above, Horowitz only discloses administration of liquid compositions of omeprazole, not solid compositions. Thus, even if combined, Nomura and Horowitz fail to disclose a method of treating a gastric acid related disorder with a solid pharmaceutical composition that meets the PK limitation(s) claimed by Patentee.

For the foregoing reasons, Patentee submits that no *prima facie* case of obviousness has been established and respectfully requests withdrawal of this rejection.

VI. Rejection of Claims 1-11, 14 and 19-25 Under §103(a) Over Upson in View of Bengtsson and Horowitz

Claims 1-11, 14, and 19-25 stand rejected under 35 U.S.C. §103(a) as unpatentable over Upson in view of Bengtsson and Horowitz. Patentee respectfully traverses this rejection.

As discussed above, where a proposed combination would render a prior art reference unsatisfactory for its intended purpose, the resulting inoperable prior art reference may be considered to teach away from the proposed combination. *See, e.g.*, MPEP §2143.01 V.; *In re Gordon*, 733 F.2d 900 (Fed. Cir. 1984). Here, Upson describes a pharmaceutical composition comprising an agent for treating upper GI distress and 3-1-methoxy propane 1,2-diol in amounts effective *for providing a cooling sensation to the throat*. *See* Upson at abstract. In order to provide a cooling sensation in the throat, the cooling agent must of course be exposed to the throat. Combination of Upson with Bengtsson would necessarily prevent this intended purpose because Bengtsson discloses pharmaceutical formulations that are *completely covered by an enteric coat*. *See id.* at Col. 2, ll. 31-34. Bengtsson's enteric coat prevents any of the contents of the formulation from being exposed to the throat or GI tract until the composition reaches the duodenum. Combination of Upson's compositions with the teachings in Bengtsson would result in a composition that was completely enteric coated, thereby preventing exposure of Upson's cooling agent to the throat. This would render Upson unsatisfactory for its intended purpose of providing a cooling sensation to the throat. As such, these references teach away from their combination and no *prima facie* case of obviousness has been established. Horowitz

does not remedy this defect. Horowitz is directed to liquid dosage forms that could not be enteric coated as per the teachings of Bengtsson.

Patentee further submits that the instant rejection is based on impermissible hindsight picking and choosing of prior art elements. Obviousness is tested by "what the combined teachings of the references would have suggested to those of ordinary skill in the art." *In re Keller*, 642 F.2d 413 (CCPA 1981). It "cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination." *ACS Hosp. Sys., Inc. v. Montefiore Hospital*, 732 F.2d 1572 (Fed. Cir. 1984). The "teachings of references can be combined *only* if there is some suggestion or incentive to do so." *Id.* One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to depreciate the claimed invention. *In re Fine*, 837 F.2d 1071 (Fed. Cir. 1988).

In the present case, the Examiner correctly indicates that Upson does not recite the claimed amounts of proton pump inhibitor or ratio between proton pump inhibitor and buffering agent. But, the Examiner asserts that since Bengtsson discloses daily amounts of magnesium omeprazole in the amount of 1-400 mg and that magnesium omeprazole may be stabilized with an alkaline reacting substance, it would have been obvious to combine the two references to arrive at the presently claimed invention. This is classic impermissible hindsight picking and choosing of the almost infinite number of possible combinations of dosage forms, ingredients and amounts in view of the art recognized unpredictability of achieving success.

Bengtsson, at most, teaches that minute amounts of an alkaline reacting compound can be used to protect enteric coated magnesium omeprazole. This disclosure provides no motivation to arrive at the presently claimed invention which (1) includes non-enteric coated proton pump inhibitors; (2) a recited total buffering agent to total PPI weight ratio; and (3) a specific PK profile of the proton pump inhibitor.

The Examiner also states that the claimed PK limitation is an inherent property of Bengtsson and Upson as evidenced by Horowitz. Applicants respectfully disagree. Bengtsson and Upson provide no indication or suggestion of the PK performance of their solid formulations. Horowitz provides no indication or suggestion of the PK performance of a solid pharmaceutical composition. As such, the PK performance of a solid pharmaceutical composition as presently claimed was heretofore unknown and unpredictable prior to Patentee's invention. Again, inherency and obviousness are distinct legal concepts, and obviousness cannot

be predicated on what is unknown. *In re Spormann* 363 F.2d 444 (CCPA 1966) and *In re Dillon*, 919 F.2d 688 (Fed. Cir. 1990) (en banc). Thus, withdrawal of the instant rejection is respectfully requested.

Furthermore, the combination of Upson and Bengtsson do not teach or suggest each element of the claimed invention. Specifically, Upson and Bengtsson do not disclose compositions comprising at least some PPI that is not enteric coated. In fact, Bengtsson actually teaches away from the claimed invention, which requires at least some non-enteric coated PPI: "A pharmaceutical oral solid dosage form of omeprazole must be protected from contact with acidic gastric juice by an enteric coating." Bengtsson at Col. 1, ll. 45-47. Moreover, Horowitz only discloses administration of liquid compositions of omeprazole, not solid compositions. As discussed above, the pharmacokinetic profile of an enteric coated dosage form and a liquid dosage form are quite different.

Thus, even if combined, Epson and Bengtsson fail to disclose a method of treating a gastric acid related disorder with a solid pharmaceutical dosage form comprising at least some proton pump inhibitor that is not enteric coated and which meets the claimed PK limitation(s).

For the foregoing reasons, Patentee submits that no *prima facie* case of obviousness has been established and respectfully requests withdrawal of this rejection.

VII. Rejection Of Claims 12-13 And 15-18 Under 35 U.S.C. § 103(A) As Allegedly Unpatentable Over Upson In View Of Bengtsson And Horowitz

Claims 12-13 and 15-18 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Upson in view of Bengtsson and Horowitz and further in view of Martindale. Patentee submits that there is no motivation to combine these reference teachings so as to arrive at the claimed invention, and even if combined, the references fail to teach or suggest each limitation of the claims, and, therefore, respectfully requests withdrawal of this rejection.

These references have been discussed above and need not be repeated here. Further, because claims 12-13 and 15-18 are dependent on claim 1, even if the references are combined in the manner suggested by the Examiner, they still fail to teach or suggest each element of the claimed invention.

For the foregoing reasons, Patentee submits that no *prima facie* case of obviousness has been established and respectfully requests withdrawal of this rejection.

B. OBJECTIVE EVIDENCE OF NON-OBVIOUSNESS

Although Patentee disagrees with any conclusion that a *prima facie* case of obviousness has been established for one or more of the above claims, Patentee submits herewith objective evidence of non-obviousness. Evidence rising from "secondary considerations" *must always* when present be considered en route to a determination of obviousness. MPEP § 716.01(a). Furthermore, "[a]ll of the competent rebuttal evidence *taken as a whole* should be weighed against the evidence supporting the *prima facie* case. *In re Piasecki*, 745 F.2d 1468, 1472, 223 USPQ 785, 788 (Fed. Cir. 1984). (emphasis added).

1. **Proceeding Contrary to Accepted Wisdom.**

Proceeding contrary to accepted wisdom in the art is evidence of non-obviousness. See *In re Hegdes*, 783, F.2d 1038, (Fed. Cir. 1986). For example, in a 1996 reference by Herling et al., the authors state that "due to their inherent-chemical instability in acidic conditions, PPI's such as omeprazole, lansoprazole, etc. *have to* be administered orally as *enteric coated formulations* which prevent acidic degradation during passage through the stomach." Herling AW, Weidman K., "*Gastric proton pump inhibitors*" in Burgers' Medicinal Chemistry and Drug Discovery 1996: 119-151. See also e.g., *Astra Ag v. Andrx Pharmaceuticals, Inc.*, 222 F. Supp. 2d 423 (S.D.N.Y. 2002). ("Overcoming omeprazole's multiple sensitivities proved to be a substantial challenge, and Astra considered a number of different approaches to make an oral formulation") (attached as Exh. 7). Astra, therefore, concluded that the only commercially viable option was to enteric coat its product.

Even the references relied on by the Examiner demonstrate Patentee's procession against conventional wisdom. For example, Depui states that "it is obvious that the one of the active substances being a proton pump inhibitor *must be* protected from contact with acidic gastric juice by an enteric coating layer." p. 3, ll. 27-28 (emphasis added). Therefore, according to Depui, it was *mandatory* to one of ordinary skill in the art that proton pump inhibitors such as omeprazole had to be enteric coated to protect against gastric acid induced degradation. As another example, Bengtsson states:

From what is said about the stability properties of omeprazole, it is obvious that an oral dosage form of omeprazole must be protected from contact with the acid reacting gastric juice and the active substance must be transferred in intact form to that part of the gastrointestinal tract where pH is near neutral and where rapid absorption of omeprazole can occur. A pharmaceutical oral dosage form of

omeprazole must be protected from contact with acidic gastric juice by an enteric coating.

Bengtsson at Col. 1, ll. 38-48. Thus, prior to Patentee's claimed invention, those of skill in the art thought that PPIs had to be enteric coated in order to protect them from acid degradation in the stomach.

2. License Showing Industry Respect for Invention.

In addition, licenses showing industry respect for a claimed invention are objective evidence of non-obviousness. *Arkie Lures, Inc., v. Gene Larowe Tackle, Inc.*, 119 F.3d 953 (Fed. Cir. 1997) and *Pentec, Inc., v. Graphic Controls Corp.*, 776 F.2d 309 (Fed. Cir. 1985). In the present case, Patentee entered into a license agreement with Santarus, Inc., under which Santarus received the exclusive world-wide rights to make, use and sell, have made, have sold, offer for sale and import products under certain and future patent rights covering the invention, including rights under the instant patent. (Exh. 8). Pursuant to this license, Santarus has made significant expenditures related to the commercialization of its Zegerid® (omeprazole/sodium bicarbonate) products, which are covered by the '885 Patent. As part of its support for those activities, Santarus raised net proceeds of more than \$80 million as a private company and net proceeds of more than \$130 million in connection with its initial public offering and in subsequent financings. (Exh. 9). Zegerid® Capsules and Powder for Oral Suspension are presently marketed in the United States by Santarus.

CONCLUSION

For the foregoing reasons, Patentee request withdrawal of the instant rejections. Should the Examiner have any questions, she is encouraged to contact the undersigned.

Respectfully submitted,



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